PROTEIN INTERACTION MAPPING AND COMPUTER AIDED DRUG DESIGNING FOR NEURODEGENERATIVE DISEASES

Submitted by

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Synopsis

Significant health risks are associated with neurodegenerative disorders. A variety of age-related factors have developed recently with the increase in the older population. These illnesses are characterised by the accumulation of proteins with altered physicochemical properties and the progressive degradation of neurons in the peritoneal and brain tissues. Some of the most challenging issues that modern nations face as their populations get older are Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis, Parkinson's, Huntington's, and Alzheimer's are some of the most difficult problems that contemporary countries deal with as their population's age. To find novel PPIs that could aid in the pathophysiology of neurodegenerative illnesses, employ computational and experimental methods. After outlining the benefits and drawbacks of the present viewpoint, we address a number of findings within the framework of recent research, pose further queries, and provide succinct closing thoughts. The String database was used to identify protein-protein interactions between targets for neurodegenerative diseases that overlapped and were therefore considered to be potential targets. These disorders are linked to four different gene types: APBA2, TARDBP, HTT, and SNCA. Twenty possible neurodegenerative diseases were present in all. SNCA protein is a major risk factor for the development of PD. But, little is understood about how the human SNCA gene is transcriptionally regulated in vivo in the brain. PD research has led to the development of new therapies, such as deep brain stimulation, gene therapy, and immunotherapy. Neuroprotective drugs are those that bind to α-synuclein and produce a loop structure between the N- and C-terminus; neurotoxic drugs are those that cause a more compact structure. Finding many medications that can bind to both N- and C termini, strengthening this interaction and preventing Alpha-syn misfolding, may not come as a surprise. In order to comprehend the molecular mechanisms underlying Parkinson's disease (PD) and possibly find biomarkers or therapeutic targets, a thesis on gene expression analysis of PD would probably concentrate on detecting and characterising altered gene expression patterns in PD patients relative to healthy controls. Analysing gene expression in various PD-affected brain areas, researching blood-based gene expression signatures, and investigating the influence of genetic and epigenetic variables on gene expression in PD are some examples of this scope. Examining blood sample gene expression to find possible biomarkers that may be applied to early diagnosis or illness progression tracking. Identifying DEGs that are consistently changed in Parkinson's disease by comparing the gene expression patterns of PD patients and

healthy controls and identify the cellular pathways where DEGs are abundant, which will shed light on the fundamental processes of Parkinson's disease. To comprehend how changed gene expression may impact cell processes in Parkinson's disease, genes are categorised according to their functional functions and cellular components. The relationships between the proteins that DEGs encode in order to find possible hub genes and signalling pathways that are thrown off balance in Parkinson's disease. While CTCF controls the formation of its enhancer-promoter loops, THAP1 regulates the SNCA intronic enhancers activities. PPI networks have been built, gene set enrichment analysis was carried out using Cluster Profiler and Path view, and cluster analyses were carried out in Cytoscape using String and MCODE. ClueGO software was used to conduct functional enrichment evaluation of the generated sub networks. The CytoHubba approach had been utilized to identify the hub genes in both scenarios. Ten hub genes that were found to be strongly upregulated were SST, CRH, OPRM1, GRM5, RGS7, HTR2A, RGS7BP, HTR1E, MC4R, and IGF1. Ten hub genes that were found to be greatly downregulated were HOXA5, HOXA7, HOXB6, HOXB5, HOXB8, HOXB9, HOXA10, HOXA9, and S100A6. It was established how often PINK1 mutations were in control people, community-based patients with idiopathic Parkinson disease (PD) (non-familial PD), and familial parkinsonism.Clinical and demographic characteristics of those without PINK1 mutations or those with homozygous or heterozygous PINK1 variations. Young-onset Parkinson disease of the PINK1 type often responds well to L-dopa and/or other dopamine agonists, which can be used in conjunction with amantadine, anticholinergics, monoamine oxidase-B inhibitors, and catechol-O-methyltransferase inhibitors. Speech therapy, occupational therapy, and/or physical therapy are used to maintain and/or enhance fine and gross motor abilities. The project could investigate whether certain mutations are associated with the clinical manifestation of Parkinson's disease (PD), including the age at which symptoms first appear, their intensity, and how well they respond to therapy. The results of this study may help manage neurodegenerative diseases and aid in the future therapy of PD. Hereditary Parkinson's disease mostly is caused by mutations in the PARK2 and PARK6 genes. Parkin, an E3 ubiquitin ligase, and PTEN-induced kinase 1 (PINK1), a protein kinase, are each encoded by these genes. Parkin and PINK1 work together to control the mitophagy process, which recycles harmed mitochondria after oxidative stress. The RBR family of E3 ubiquitin ligases includes Parkin. The IBR domain is located at the parkin protein's C terminal edge. A novel homozygous mutation (Q126P) in PINK1 gene was reported in two German sisters diagnosed with a clinical presentation resembling Parkinsonism. The structural aspect of (Q126P) mutation was studied here. Research has

looked at new compounds for naturally occurring antioxidant phytochemicals that may treat PD patients through their neuroprotective mechanism by addressing oxidative stress, neuroinflammation, abnormal protein accumulation, mitochondrial dysfunction, endoplasmic reticulum stress, deficit in neurotrophic factor, and apoptosis. α-synuclein mutations only partially explain PD in the general population, α-synuclein is prominently implicated in idiopathic PD due to the development of Lewy bodies and dystrophic neuritis. Subsequently, α-synuclein immune staining showed several inclusions that were previously undetected by conventional histological techniques. While both fibrillar and oligomeric forms of α-synuclein have been demonstrated to be harmful, current research indicates that the more toxic forms that cause cell death in Parkinson's disease are protofibrils and oligomers that develop early in the aggregation process. On the other hand, it seems that α-synuclein fibrils are the most effective in multiplying, which aids in the disease's development and dissemination.It is unknown to what degree these oligomers replicate the structure and characteristics of those discovered in brain tissue from Parkinson's disease patients because the majority of investigations that validate the harmful consequences of various . α-synuclein assemblies have employed in vitro produced species. Mutations, post-translational modifications, a divergence between the α-synuclein synthesis and degradation, and environmental factors all affect.α-synuclein propensity to aggregate. Phytochemicals, derived from plants, have shown promise as potential therapeutics for PD. Using MD modelling; the protein folding investigation may reveal the protein conformations linked to alpha synuclein protein, which might be useful for future drug development. Provide a computational framework for prospective assessment and identification. This work thoroughly assesses naturally occurring phytochemicals with neuroprotective or therapeutic potential in Parkinson's disease (PD) using *in-silico* techniques such as molecular docking and molecular dynamics simulations. These results highlight the potential of phytocompounds as PD treatment options and call for more *in vitro* and *in vivo* research to confirm their effectiveness. This strategy offers hope for creating innovative therapies that focus on the fundamental molecular causes of Parkinson's disease. Alpha synuclein protein and natural phytochemical complexes were examined in depth from a molecular perspective. In the current study, we attempted to use MD simulations and computational molecular docking to examine the regulatory functions of the alpha synuclein protein. Specific amino acid residues of alpha synuclein, specifically the basic amino acid residues from amino acid residues 1-61, bind to the major amino acid residues Lys32, Glu35, Gly36, Leu38, Val40, Lys43, Thr44, Lys45, Glu46, Gly47, and Val48 were identified by MD simulations. These findings

corroborate earlier experimental investigations. The N-terminal residues were discovered by this MD simulation investigation. By docking eight natural and ten AI-based ligands with the alpha synuclein protein. Our investigation revealed that the ligand4 would assist to suppress the disease condition of Parkinson's disease, based on a prior study about the potential regulatory role of various natural phytochemicals that are significant for Parkinson's disease.